Remarks

Prior to the submission of this Response, claims 46-72 were pending in this application. No amendments are made herein; Applicants provide the Listing of Claims solely for Examiner Huff's convenience. After entry of this Response, **claims 46-72 continue to be pending**.

REQUEST FOR CONTINUED EXAMINATION

Applicants thank Examiner Huff for acknowledging that prosecution of this application has been reopened and that claims 46-72 are pending.

EXAMINER INTERVIEW

Applicants also thank Examiner Huff for the courtesy of a telephone interview with their representative Dr. Anne Carlson on April 21, 2009, during which the rejections against the pending claims were discussed. Although no consensus was reached regarding the claims, Applicants believe that the arguments put forth herewith fully address the pending rejections.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 60-62 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because it is not clear what the activity is that is being enhanced. Applicants traverse this rejection.

Claim 60 recites "increased activity of the immune cell, wherein the increased activity is increased tumor immunosurveillance." As the enhanced activity of the immune cell is equated with increased tumor immunosurveillance, Applicants respectfully submit that it is clear what activity is being enhanced. Applicants further submit that claim 60 corresponds to original claim 26 (now canceled), which was previously rejected under 35 U.S.C. §112, second paragraph as allegedly it was "not clear what activity of the immune cell is enhanced" (June 8, 2007 Office action at page 2). The Office later withdrew the rejection of claim 26 once it was amended to include the phrase "increased activity of the immune cell, wherein the increased activity is increased tumor immunosurveillance" (see May 15, 2008 Office action at page 2). As current claim 60 contains the claim language that the Office acknowledged rendered claim 26 clear and

definite, it is believed that current claim 60 also fulfills the requirements under 35 U.S.C. §112, second paragraph. In view of the above discussion, Applicants submit that claim 60 is clear and definite and withdrawal of the rejection is respectfully requested. Claims 61 and 62 depend from claim 60 and incorporate all the limitations thereof.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

(I) Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.*

Claims 46-50, 52-55, 59-67, 69, and 71 are rejected under 35 U.S.C. §103 as obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of PCT Application No. WO 00/01410, Barbera-Guillem (U.S. Patent No. 6,224,866), Rosenblum (U.S. Patent Application No. 2005/0214307), and Zavada *et al.* (U.S. Patent No. 6,297,041) because the combination of references allegedly teaches that "compounds that treat tumors can also be used to treat tumor recurrence" (Office action at page 4). Applicants strenuously traverse this rejection.

(a)The Cited References

Dasch *et al.* (i) discloses the use of a TGF-beta antagonist (the 1D11.16 monoclonal antibody) to *regress existing tumors* (column 5, lines 54-58), to *treat* tumor cells that produce TGF-beta (column 2, lines 28-32), and to *treat* metastatic cancers (column 2, lines 33-37), and (ii) claims a method of inhibiting the growth of tumor cells (claim 1). Dasch *et al.* does not teach the use of the disclosed TGF-beta antagonists to *inhibit the recurrence* of a tumor, not could this be inferred from the reference. In this regard, Dasch *et al.* does not disclose the concept of tumor recurrence, nor would it be known from the teachings of Dasch *et al.* that the disclosed TGF-beta antagonists could inhibit tumor recurrence.

Barbera-Guillem discloses the use of an immunotherapeutic composition that binds directly to B cells (for example, anti-CD20, anti-Lym-1, or anti-CD19 antibodies) in order to cause B cell depletion and reduce a pro-tumor immune response (see for example, column 3, line 1 through column 4, line 14; column 5, lines 57-63). Barbera-Guillem also discloses that the same agent can be used to *treat* both a primary tumor and a recurrence. However, Barbera-Guillem does not teach that the disclosed agents can *inhibit* tumor recurrence, not does it teach anything about the 1D11 antibody or any antibody that can bind soluble TGF-beta.

WO 00/01410 discloses "that antagonizing the effects of TGF-β1 suppresses tumor growth *in vivo* through an anti-angiogenic mechanism" (WO 00/01410, page 3, lines 19-20). WO 00/01410 also discloses that the anti-TGF-beta antibodies can be used "to detect or quantify the TGF-β" and that the "[r]esults from these tests can be used to diagnose or predict the occurrence of recurrence of a cancer" (WO 00/01410, page 24, lines 7-9; emphasis added). However, there is no teaching in WO 00/01410 that anti-TGF-beta antibodies can be used to *treat* or *inhibit* recurrence and it does not teach the 1D11.16 antibody.

Zavada *et al.* discloses the use of (i) antibodies directed against an oncoprotein (the MN protein) to *treat* cancer patients expressing the MN protein (column 10, lines 42-44) and (ii) anti-idiotype antibodies to MN-specific antibodies in a vaccine to *inhibit recurrence* of a MN-expressing tumor (column 10, lines 5-9). As the anti-idiotype antibodies are MN protein mimics, the anti-MN protein antibody and the anti-idiotype antibody are completely different agents.

Rosenblum discloses that one specific agent (an immunoconjugate comprised of a single chain antibody linked to a cytotoxic moiety, where the antibody moiety recognizes the cell surface protein GP 240 and thereby targets the cytotoxic moiety to a tumor cell expressing this antigen) used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). The sole purpose of the antibody moiety in the Rosenblum agent is to target the cytotoxin (the active, anti-tumor component of the immunoconjugate) to the GP 240-expressing tumor cell (paragraph [0015]). Thus, the "antibody" disclosed in Rosenblum is not, *per se*, preventing the tumor recurrence; it is simply targeting the anti-tumor cytotoxin to the tumor cell. Rosenblum does not disclose the 1D11.16 antibody or any another antibody that inhibits TGF-beta activity.

(b) Claims are directed to a method of ***inhibiting*** *a tumor* ***recurrence***

Applicants remind the Examiner that the pending claims are directed to methods of *inhibiting* a tumor recurrence and not to *treating* a tumor recurrence. As discussed in the Declaration under 37 C.F.R. 1.132, from Inventor Jay A. Berzofsky, M.D., Ph.D. (Declaration) provided herewith, "the actions of "inhibiting" and "treating" are very different, as methods of

inhibiting a tumor recurrence are prophylactic and are used to prevent a tumor from *developing*, whereas methods of treating a tumor recurrence are directed against an *existing* tumor" (Declaration at paragraph 3). Moreover, it is well known in the art that "the effectiveness of an agent for *treating* a tumor recurrence does not predict the effectiveness of the same agent for *inhibiting* the recurrence" (Declaration at paragraph 3; see also Declaration at paragraphs 5 and 6). Thus, Applicants strenuously submit that the phrase "treating a recurrence" cannot be equated with "inhibiting a recurrence" and a reference that only discloses that an agent can be used to *treat* a tumor recurrence does not teach *inhibiting* tumor recurrence.

The Office action dated May 12, 2008, alleges that "applicant defines treatment as including prophylactic inhibition" and therefore "equates treatment to inhibition/prevention" (May 12, 2008 Office action at pages 4 and 5). Applicants disagree, for the reasons already discussed above and for the following reasons. The "generic word "treatment" is an all-purpose term that refers to many things, including the use of both agents and therapies to inhibit or treat a disease in a subject" (Declaration at paragraph 4). The specification at page 17, lines 11-14, states that treatment "[r]efers to **both** prophylactic inhibition of disease (such as tumor recurrence) and therapeutic interventions to alter the natural course of an untreated disease process, such as a tumor growth. Treatment of a tumor **includes**, for instance, the surgical removal of the tumor. Treatment of a tumor can also **include** chemotherapy, immunotherapy, or radiation therapy. Two or more methods of treating a tumor can be provided to a subject in combination. Treatment of a subject **includes** inhibiting or measurably reducing the recurrence of a tumor" (emphasis added). "As treatment encompasses both inhibition and intervention, treatment **cannot be equated exclusively** with inhibition" (Declaration at paragraph 4; emphasis added). Thus, Applicants strenuously submit that the specification does not define *treatment* as being equivalent to *inhibition*, nor should the Office interpret these terms to be equivalent.

The Office action dated May 12, 2008 alleges that the "definition of 'therapeutically effective amount of an agent' gives an example of using the same anti-TGF-beta antibody to treat and inhibit tumor recurrence (see page 16, lines 32-33)" (May 12, 2008 Office action at page 5). Applicants respectfully point out that the Office has unnecessarily narrowly interpreted this passage from the specification. The specification at page 16, lines 32-33, states that "the

amount of neutralizing anti-TGF-β antibody that, when administered to a subject following treatment of a tumor, can inhibit recurrence of the tumor." This is not a statement that the neutralizing anti-TGF-β antibody itself is administered to treat an existing tumor. Rather, the point of the statement is to acknowledge that the neutralizing anti-TGF-β antibody can be used to inhibit recurrence of the tumor following any treatment of a tumor (surgery, chemotherapy, immunotherapy, radiation therapy etc.). Accordingly, the cited passage does not support the Office's assertion that Applicants have equated treatment exclusively with inhibition.

Applicants also remind the Examiner that the biology of a primary tumor and a recurrent tumor are very different. It is well known in the art that an agent that is used to treat a primary tumor or a metastasis may not be effective at treating a tumor recurrence (see the Amendment and Response submitted on April 8, 2008 and accompanying Declaration under 37 C.F.R. 1.132, from Inventor Jay A. Berzofsky, M.D., Ph.D.). Accordingly, the phrase "treating a tumor" cannot be equated with "treating a tumor recurrence" or "inhibiting a tumor recurrence" and a reference that only discloses that an agent can be used to treat a *tumor* does not teach either inhibiting or treating *tumor recurrence*.

As "treatment" cannot be equated with "inhibition" and "tumor" cannot be equated with "tumor recurrence," Applicants submit that the Office's statement that "it is known in the art that that compounds that *treat tumors* can also be used to *treat* tumor *recurrence*" (Office action at page 4; emphasis added) is both inaccurate and irrelevant to the pending claims, which are specifically directed to methods of **inhibiting** tumor **recurrence**.

(c) The Rejection Vis-à-Vis the Cited References

In order to support a conclusion that a claimed invention is obvious, the United States Patent and Trademark Office (USPTO) must show (i) that all the claimed elements were known in the prior art and (ii) that combining the elements would have yielded predictable results to one of skill in the art. Thus, once it is determined that all of the claimed elements are present in the prior art, the predictability of the claimed combination can be addressed. With regard to the latter, the USPTO has provided Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*

Based on those Guidelines, the Office must provide the appropriate rationale to support rejections under 35 U.S.C. §103. More specifically, the Guidelines provide the following non-exclusive rationales for supporting a finding that a claimed invention is obvious (with emphasis added):

(A) combining prior art elements according to known methods to yield **predictable** results;

(B) simple substitution of one known element for another to obtain **predictable** results;

(C) use of **known** technique to improve similar devices (methods, or products) in the same way;

(D) applying a **known** technique to a known device (method, or product) ready for improvement to yield **predictable** results;

(E) "obvious to try" - choosing from a finite number of identified, **predictable** solutions, **with a reasonable expectation of success**;

(F) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been **predictable** to one of ordinary skill in the art; and

(G) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The emphasis in the Guidelines is accordingly the **predictability** of the combination, as a basis for a finding that there is a reasonable expectation of success of obtaining the Applicants' invention associated with a prior art combination. It is respectfully submitted that in the present case, there is no such element of predictability in the purported combination of references, and accordingly no reasonable expectation of success.

As admitted in the current Office action, Dasch *et al.* does not discuss the treatment of tumor recurrence (nor does Dasch *et al.* disclose methods of *inhibiting* tumor recurrence). However, the current Office action combines Dasch *et al.* with four other references (WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.*) that allegedly make up for the deficiency of Dasch *et al.* Applicants respectfully disagree. In view of the current USPTO Guidelines regarding obviousness, Applicants submit that (i) the cited references do not teach all

of the elements of the claimed invention (they do not make up for the deficiencies of Dasch *et al.*) and (ii) the teachings of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* could not have been combined to **predictably** yield the claimed invention. WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* each disclose antibodies, but that is where the similarity with Applicants' claimed methods ends.

WO 00/01410 discloses "that antagonizing the effects of TGF-β1 suppresses tumor growth *in vivo* through an anti-angiogenic mechanism" (WO 00/01410, page 3, lines 19-20). WO 00/01410 also discloses that the anti-TGF-beta antibodies can be used "to detect or quantify the TGF-β" and that the "[r]esults from these tests can be used to diagnose or predict the occurrence of recurrence of a cancer" (WO 00/01410, page 24, lines 7-9; emphasis added). Thus, this reference teaches that the antibody can be used to quantify the amount of TGF-beta as a measure of potential recurrence, rather than using the disclosed antibody to inhibit tumor recurrence. The Office alleges that simply because WO 00/01410 discloses that antibodies to TGF-beta can "be used in the diagnosis and treatment of proliferating cells and that the diagnosis also includes diagnosing tumor recurrence . . . one of ordinary skill in the art would immediately envisage that the same antibody that can detect rumor recurrence can also be used in treatment of tumor recurrence" (Office action at page 5). However, there is no teaching in WO 00/01410 that a detectable level of TGF-beta is a specific marker of recurrence or that anti-TGF-beta antibodies can be used to *inhibit* recurrence, specifically. It is well known in the art that "antibodies are unpredictable" (Declaration at paragraph 7) and, as discussed above, it is not predictable that an agent used to **treat** a tumor or a tumor recurrence will be effective at **inhibiting** a tumor recurrence. Thus, Applicants strenuously submit that "one of skill in the art would not be able to predict that an antibody used for **detection** also would be effective at **inhibition** of tumor recurrence, without first having demonstrated that the antibody can function to both detect and inhibit tumor recurrence" (Declaration at paragraph 7; emphasis added), nor would one of skill in the art equate "detection" with "inhibition." A clear example is that "antibodies to Prostate Specific Antigen (PSA) can be used to measure PSA levels to monitor tumor progression or detect or predict tumor recurrence, but these anti-PSA antibodies cannot be used to treat, prevent, or inhibit tumor recurrence" (Declaration at paragraph 7). Accordingly, WO 00/01410 is not **predictive** of Applicants' use of this antibody to inhibit tumor recurrence.

Barbera-Guillem discloses the use of an immunotherapeutic composition that binds directly to B cells (for example, anti-CD20, anti-Lym-1, or anti-CD19 antibodies) in order to cause B cell depletion and reduce a pro-tumor immune response (see for example, column 3, line 1 through column 4, line 14; column 5, lines 57-63). Barbera-Guillem does not teach the 1D11.16 antibody, nor does it teach any other antibody that can bind soluble TGF-beta. In contrast to the antibodies disclosed in Barbera-Guillem, the 1D11.16 antibody of the claimed methods does not bind B cells or deplete B cells; rather, it binds TGF-beta which is released from non-T-non-B cells (see, for example, the specification at page 31, lines 26-29). More specifically, the 1D11 antibody blocks an immunosuppressive effect of TGF-beta in order to increase immunosurveillance by B cells or T cells (see, for example, page 19, lines 23-32 and Example 5). In other words, the 1D11.16 antibody acts to increase the biological activity of B cells and T cells, whereas the antibody disclosed in Barbera-Guillem effectively acts to decrease the biological activity of B cells by depleting them. Moreover, as the antibodies disclosed in Barbera-Guillem function by a completely different mechanism than the 1D11.16 antibody, Barbera-Guillem teaches away from using an antibody to increase the biological activity of B cells and T cells. Thus, the antibodies disclosed in Barbera-Guillem provide no reliable guidance for the activities exhibited by the 1D11.16 antibody, nor are they at all **predictive** of Applicants' use of this antibody. Furthermore, as Barbera-Guillem does not teach that the same agent can be used to both treat and inhibit tumor recurrence, this reference does not overcome the deficiencies of Dasch *et al.*

Rosenblum discloses that one specific agent used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). The "agent" of Rosenblum is an immunoconjugate comprised of a monoclonal antibody or a single chain antibody linked to a cytotoxic moiety, where the antibody moiety recognizes the cell surface protein GP 240 and thereby targets the cytotoxic moiety to a tumor cell expressing this antigen (paragraph [0013]). The sole purpose of the antibody moiety is to target the cytotoxin (the active, anti-tumor component of the immunoconjugate) to the GP 240-expressing tumor cell (paragraph [0015]). Thus, the "antibody" disclosed in Rosenblum is not, *per se*, inhibiting the tumor recurrence; it is simply targeting the anti-tumor cytotoxin to the tumor cell. Rosenblum does not disclose the

1D11.16 antibody or another antibody that inhibits TGF-beta activity. The mere fact that Rosenblum (or any reference) discloses an antibody that targets a tumor protein is not, on its own, predictive of Applicants' claimed methods, which use a completely different antibody in an unpredicted application. In contrast to the agent of the Rosenblum disclosure, the anti-TGF-beta antibody of the claimed method does not target the tumor cell at all, but rather removes an inhibitor that is blocking an immune response. Thus, nothing about the Rosenblum agent would provide reliable guidance to one of ordinary skill in the art for the activities exhibited by the 1D11.16 antibody, nor is it **predictive** in any way of Applicants' use of this antibody.

Finally, as discussed above, Zavada *et al.* discloses the use of antibodies directed against an oncoprotein (the MN protein) to *treat* cancer patients expressing the MN protein (column 10, lines 42-44). Zavada *et al.* also discloses the use of a different agent, anti-idiotype antibodies to MN-specific antibodies (mimics of the MN protein), in a vaccine to *inhibit recurrence* of a MN-expressing tumor (column 11, lines 5-9). However, the assertion by the Office that "Zavada *et al.* discloses [that] the same compounds (which include polypeptides and antibodies) can be used for treatment and [inhibition] of recurrence" (Office action at page 5) is not appropriate when relevant to the invention, as claimed, because the claims are directed to one specific antibody having a specific function, not to an entire class of compounds (antibodies), each having a different function. For example, although an anti-MN antibody and an anti-idiotype antibody are both antibodies, they are different antibodies that bind different antigens and have different functions (treating a tumor or inhibiting a recurrence). As Zavada *et al.* does not teach that one specific agent can be used to both treat a tumor and inhibit a recurrence, one of skill in the art **would not have predicted** the claimed method in view of this reference.

In summary, Dasch *et al.* does not disclose treating or inhibiting tumor recurrence with 1D11.16 or any other antibody. Applicants respectfully submit that the disclosures of WO 00/01410, Rosenblum, and Zavada *et al.* are not relevant to the claimed invention and should not be combined with Dasch *et al.* Barbera-Guillem does not overcome the deficiencies of Dasch *et al.* Furthermore, Applicants submit that the disclosures of WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are not predictive that an antibody which blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor and these references,

therefore, cannot be combined with Dasch *et al.* to make up for the deficiencies of this reference. Accordingly, Applicants submit that claims 46-50, 52-55, 59-67, 69, and 71 are not obvious in view of the discussion set forth above, and request that this rejection be withdrawn.

(II) Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.*, and Suthanthiran *et al.*

Claims 46-55 and 59-72 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.,* and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333). Applicants respectfully traverse this rejection.

The Office action states that Suthanthiran *et al.* discloses the use of TGF-beta antagonists, including monoclonal antibodies, "to *treat* a variety of different cancers known to be associated with TGF-beta" (Office action at page 7, emphasis added). However, Suthanthiran *et al.* **does not** teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. Nor does Suthanthiran *et al.* disclose the concept of tumor recurrence. Thus, Suthanthiran *et al.* does not make up for the deficiencies of Dasch *et al.*

As discussed above, the disclosures of WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are not predictive that an antibody that blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor. Moreover, the disclosures of WO 00/01410, Rosenblum and Zavada *et al.* are not relevant to the claimed invention. Dasch *et al.* and Suthanthiran *et al.* do not, on their own, implicitly or explicitly teach all elements of the claimed methods. Thus, Applicants' claims are non-obvious over the combination of cited references. Withdrawal of this rejection is requested.

(III) Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.*, and Terabe *et al.*

Claims 46-72 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.,* and Terabe *et*

al. (*Nature Immunology*, 1:515-520, 2000). Applicants respectfully traverse this rejection to the extent it might be applied to the pending claims.

The Office action states that Terabe *et al.* shows that the "assays of claims 56-58 are known in the art . . . and are used in tumor immunosurveillance" (Office action at page 9). However, this teaching is immaterial because Terabe *et al.* **does not** teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. As discussed above, Dasch *et al.* does not teach methods of inhibiting tumor recurrence. Thus, Terabe *et al.* does not make up for the deficiencies of Dasch *et al.* In addition, as discussed above, the disclosures of WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are not predictive that an antibody that blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor and the disclosures of WO 00/01410, Rosenblum and Zavada *et al.* are not relevant to the claimed invention. Thus, these references cannot be combined with Dasch *et al.* Thus, Applicants' claims are non-obvious over the cited references. Withdrawal of this rejection is requested.

Request for Examiner Interview

Applicants believe the application is in condition for allowance and such action is requested. If the present rejections are maintained, or an additional rejection is asserted, Examiner Huff is formally requested to contact the undersigned in order to arrange a telephonic interview with her and her supervisor prior to issuance of the next Office action. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview can be arranged in advance by a written request.

Respectfully submitted,

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